Hydration Free Energies of Molecular Ions from Theory and Simulation

Maksim Misin,[†] Maxim V. Fedorov,^{*,†} and David S. Palmer^{*,‡}

[†]Department of Physics, SUPA, University of Strathclyde, 107 Rottenrow, Glasgow G4 0NG, United Kingdom

[‡]Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL, United Kingdom

S Supporting Information

ABSTRACT: We present a theoretical/computational framework for accurate calculation of hydration free energies of ionized molecular species. The method is based on a molecular theory, 3D-RISM, combined with a recently developed pressure correction (PC+). The 3D-RISM/PC+ model can provide ~ 3 kcal/mol hydration free energy accuracy for a large variety of ionic compounds, provided that the Galvani potential of water is taken into account. The results are compared with direct atomistic simulations. Several methodological aspects of hydration free energy calculations for charged species are discussed.

INTRODUCTION

Hydration free energy is the most important solvation parameter related to solubility, partitioning of compounds between different phases, and acidity and basicity constants.^{1–3} It is also widely used in the evaluation of ligand binding affinities and in various environmental models.^{4–6}

While there has been considerable progress in prediction of hydration free energy for neutral compounds, for which various methods can achieve below 1 kcal/mol accuracy,^{7–9} even the best computational models still show somewhat poor results for charged molecules.^{7,8} We note that research in this direction has been focused on implicit models, which approximate solvent as a dielectric continuum. However, these methods rely on heavy parametrization^{7,8} because they cannot provide information regarding solvent structure and neglect such important effects as solvent polarization, electrostriction, dielectric saturation, etc.^{10,11}

Explicit solvation models such as molecular dynamics (MD) provide a more realistic view of ionic solvation processes. Unfortunately calculation of solvation free energy is complicated by the need to perform simulations at many intermediate solvation stages. Also, ab initio and even polarizable charge MD is still very computationally expensive, meaning that one has to rely on approximate force fields, which have not been extensively tested nor optimized for ionic compounds. Moreover, for a long time, computation of ionic free energy has presented a substantial theoretical difficulty even with classical MD, mainly due to sensitivity of the obtained energies to the box size and the selected electrostatic method.^{10,12,13,78}

A group of semiexplicit models, such as three-dimensional reference interaction site model (3D-RISM) or classical density functional theory (CDFT), provide a nice combination of the

strengths of both explicit and implicit solvation models. They treat solvent via density correlation functions, capturing many solvation effects which are ignored by implicit models, without the need to simulate a huge number of explicit solvent molecules.^{1,14,15} Both of these models have been used to estimate solvation free energies of atomic ions, but no detailed benchmarks have been published on a series of molecular compounds that are of large interest to bioscience.^{16,17} Here we focus on 3D-RISM, partially because of a recently published pressure correction (PC+), which significantly improved the accuracy of the model,^{18,41} and partially because this method in recent years has become quite popular and has a readily available AMBER implementation.⁶⁷

This study is split into two parts. First, we compare the results obtained using the 3D-RISM/PC+ model to fixed charge molecular dynamic simulations. We note that charged solutes, unlike neutral ones, contain an additional contribution to solvation free energy that is related to the solvent Galvani potential.^{19–21} We propose a method to estimate it in the 3D-RISM framework and numerically demonstrate its validity. In the second part of the study, we compare classical force field results by the MD and 3D-RISM methods with experimental solvation free energies. In our benchmark we focus on *molecular* and not atomic ions. We show that even without taking into account effects such as water polarization or charge transfer, it is possible to obtain ionic hydration free energies with reasonable accuracy by employing commonly used force fields.

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77 ■ THEORY

78 **3D-RISM.** 3D-RISM allows one to predict the equilibrium
79 distribution of solvent around a solute without explicitly
80 sampling different system configurations. The structure of
81 solvent is described by solute–solvent site correlation
82 functions. The theory is based on the following equation

$$h_{\alpha}(\mathbf{r}) = \sum_{\beta=1}^{n_s} (\chi_{\alpha\beta} * c_{\beta})(\mathbf{r}) \quad (1)$$

84 where subscripts α and β denote indexes of sites in solvent
85 molecule, n_s is the total number of sites in solvent molecule, h_{α}
86 is the total correlation function, c_{α} is the direct correlation
87 function, and the asterisk (*) denotes convolution.^{1,14} $\chi_{\alpha\beta}$ is the
88 solvent susceptibility, typically obtained from 1D-RISM but in
89 principle also obtainable from an MD or an experimental
90 measurement.¹ In the hypernetted-chain approximation
91 (HNC), eq 1 is accompanied by the following closure

$$h_{\alpha}(\mathbf{r}) + 1 = \exp\left(-\frac{u_{\alpha}(\mathbf{r})}{kT} + h_{\alpha}(\mathbf{r}) - c_{\alpha}(\mathbf{r})\right) \quad (2)$$

93 where k is the Boltzmann constant, T is temperature, and u_{α} is
94 the potential energy between solute and solvent site α , provided
95 as an input. Both eqs 1 and 2 are written for each of the n_s
96 solvent sites. We note that these equations are approximate and
97 do not exactly reproduce solvent distributions obtained from
98 MD simulations, even when tested with the identical force
99 field.^{1,14}

100 While conceptually straightforward and thoroughly inves-
101 tigated, HNC suffers from poor computational convergence.²²
102 This problem can be reduced by the use of a partial series
103 expansion of the order n (PSE- n) of the HNC closure²³

$$h_{\alpha}(\mathbf{r}) = \begin{cases} \sum_{i=0}^n \Xi_{\alpha}^i(\mathbf{r})/i! - 1 & \text{if } \Xi_{\alpha}(\mathbf{r}) > 0 \\ \exp(\Xi_{\alpha}(\mathbf{r})) - 1 & \text{if } \Xi_{\alpha}(\mathbf{r}) \leq 0 \end{cases} \quad (3)$$

105 where $\Xi_{\alpha}(\mathbf{r}) = -u_{\alpha}(\mathbf{r})/kT + h_{\alpha}(\mathbf{r}) - c_{\alpha}(\mathbf{r})$. Typically larger n
106 values recover HNC results, while smaller n increase the
107 numerical stability of the solution. Choice of $n = 3$, denoted as
108 PSE-3, achieves a good balance between convergence and
109 accuracy and has been successfully applied in numerous
110 previous studies.^{24–26}

111 **Solvation Free Energy.** For a solute in solvent, its excess
112 chemical potential $\mu_{\text{sol}}^{\text{ex}}$ is given by Kirkwood's famous formula²⁷

$$\mu_{\text{sol}}^{\text{ex}} = \int_0^1 d\lambda \left\langle \frac{\partial U(\lambda)}{\partial \lambda} \right\rangle_{\lambda} \quad (4)$$

114 where λ is a solute coupling parameter, $\langle \cdots \rangle_{\lambda}$ indicates an
115 ensemble average at a particular λ , and $U(\lambda)$ is the potential
116 energy of the solute–solvent system. When a molecule's
117 internal degrees of freedom do not change upon phase transfer,
118 the excess chemical potential is equal to Ben-Naim's definition
119 of solvation free energy,²⁸ denoted here as simply ΔG . In this
120 work we assume that this is the case, as we are dealing with
121 primarily small molecules.

122 Equation 4 is in principle exact; direct implementation of this
123 formula in molecular simulations faces difficulties related with
124 numerical convergence and high computational costs for
125 modeling of a large number of intermediate states. Therefore,

more efficient ways to evaluate solvation free energy have been
developed in both MD- and 3D-RISM-based methods.^{1,31,78}

For MD, one can employ multistate Bennett acceptance ratio
(MBAR), a free energy estimation method which has been
shown to produce much lower error for the same number of
intermediate states between $\lambda = 0$ and $\lambda = 1$ for practically the
same computational cost.²⁹ The details of the derivation of the
method and its application have been described elsewhere.^{29,30}

When numerically evaluating ΔG_{MD} , one typically starts by
first decoupling electrostatic energy U_{Coulomb} and then
Lennard–Jones potential U_{vdW} .³¹ On the basis of this scheme
one obtains

$$\Delta G_{\text{MD}} = \Delta G_{\text{Coul}} + \Delta G_{\text{vdW}} \quad (5)$$

where ΔG_{vdW} corresponds to the process of insertion of a
molecule with partial charges set to 0 and ΔG_{Coul} corresponds
to the subsequent charging of the molecule. We note that this
equation only holds if intramolecular interactions inside solute
do not change during the whole process.

With RISM, one can skip evaluating energies at different
values of λ and obtain solvation free energy from a single-point
calculation.¹⁴ The exact form of the RISM free energy
functional depends on the closure. In the case of HNC^{14,32}

$$\Delta G_{\text{HNC}} = kT \sum_{\alpha=1}^{n_s} \rho_{\alpha} \int_V \left[\frac{1}{2} h_{\alpha}^2(\mathbf{r}) - c_{\alpha}(\mathbf{r}) - \frac{1}{2} c_{\alpha}(\mathbf{r}) h_{\alpha}(\mathbf{r}) \right] d\mathbf{r} \quad (6)$$

For PSE closure

$$\Delta G_{\text{PSE-}n} = \mu_{\text{HNC}}^{\text{ex}} - kT \sum_{\alpha=1}^{n_s} \rho_{\alpha} \int_V [\Theta(h_{\alpha}(\mathbf{r}))(\Xi_{\alpha}(\mathbf{r}))^{n+1} / (n+1)!] d\mathbf{r} \quad (7)$$

where Θ is a Heaviside step function.²³

Functionals presented above are derived from eq 4 and
contain no further approximations aside from those involved in
3D-RISM derivation.^{33,34} Unfortunately, these expressions are
known to yield severely overestimated values for hydration free
energies. A number of groups have proposed empirical
corrections to $\Delta G_{\text{3D-RISM}}$, but the scope of such corrections
remains undetermined.^{35–39}

One of the striking features of both HNC-RISM as well as
closely related CDFT in the HRF approximation is largely
overestimated solvent pressure, measured in hundreds of
atmospheres.^{25,40} Thus, a straightforward correction to over-
estimated solvation free energies predicted in both theories may
be written as^{41,42}

$$\Delta G_{\text{PC}} = \Delta G_{\text{theory}} - P_{\text{theory}} \Delta V + P_{\text{exp}} \Delta V \quad (8)$$

where PC stands for pressure correction and P_{exp} is
experimental pressure. In 3D-RISM/HNC⁴¹

$$P_{\text{HNC}} = \frac{n_s + 1}{2} \rho kT - \frac{kT}{2} \rho^2 \hat{c}(k=0) \quad (9)$$

where n_s is the number of solvent sites, ρ is the number density
of the solvent, and $\hat{c}(k=0)$ is the integral of solvent–solvent
direct correlation functions given in site–site formalism by

$$\hat{c}(k=0) = \sum_{\alpha=1}^{n_s} \sum_{\alpha'=1}^{n_s} 4\pi \int_0^{\infty} c_{\alpha\alpha'}(r) r^2 dr \quad (10)$$

Alternatively $\hat{c}(k=0)$ can be expressed using the pure solvent isothermal compressibility, χ_T , obtained during evaluation of $\chi_{\alpha\beta}$ from 1D-RISM: $\hat{c}(k=0) = 1/\rho - 1/(\rho kT\chi_T)$. We note that experimental expansion work $P_{\text{exp}}\Delta V$ in eq 8 is not strictly necessarily as at standard conditions this term is very close to 0. Recent results show that the pressure correction decreases the root-mean-square error of 3D-RISM/HNC predictions from around 16 to 4 kcal/mol for neutral organic molecules.⁴¹ Interestingly, in both theories it is not the actual PC that is most successful in predicting experimental hydration free energies but a closely related PC+ correction^{18,41,43,44}

$$\Delta G_{\text{PC+}} = \Delta G_{\text{theory}} - P_{\text{theory}}\Delta V + P_{\text{ideal}}\Delta V \quad (11)$$

where P_{ideal} is the ideal gas pressure given by $P_{\text{ideal}} = \rho kT$. Note that due to a misinterpretation, in earlier references^{18,43,44} PC+ was originally called the initial state correction or ISC. Combination of PC+ correction and 3D-RISM/HNC (also PSE-3) approximations was shown to predict hydration free energies of neutral solutes with accuracies of around 1 kcal/mol, which is comparable to MD results with the similar force field.

As yet, there is no compelling explanation of why PC+ is more accurate than PC and why it provides significant accuracy improvement for both 3D-RISM and CDFT. In ref 18 we showed that the accuracy of PC+, unlike other approximate models, is independent of temperature. Li et al. also provided arguments in support of PC+ based on asymptotic analysis,⁴⁴ but similar investigation done by Sergiievskiy et al. arrived at a different conclusion. The present work provides further support for PC+ by showing its success in application to charged molecules.

The 3D-RISM pressure, taken from ref 41, was derived for HNC closure. However, we believe it can be also used in combination with PSE-3. The difference in numerical predictions of these two closures is minimal, but the good convergence of PSE-3 makes it much more attractive for practical applications.²³ Therefore, in this paper all actual calculations are performed using PSE-3 closure.

Finally, we note that ΔG_{Coul} and ΔG_{vdW} can also be obtained using 3D-RISM.³⁸ Similarly to MD, $\Delta G_{\text{vdW}}^{\text{3D-RISM}}$ is the solvation free energy of solute with all partial charges set to 0. The Coulomb part is then

$$\Delta G_{\text{3D-RISM}}^{\text{Coul}} = \Delta G_{\text{3D-RISM}} - \Delta G_{\text{3D-RISM}}^{\text{vdW}} \quad (12)$$

Ionic Solvation Free Energy. The suggested framework for calculation of ionic solvation free energy is largely based on reviews by Hunenberger et al.¹⁰ and Lin et al.¹⁹

Solvation free energy of a single ion can be defined using two hypothetical processes (Figure 1). In the first process, referred to as a physical process, the ion is reversibly transferred from vacuum to the bulk solvent. During the transfer the ion is moved from a sufficiently large distance from the solvent, through the surface, into the bulk solution. In the second process, referred to as an unphysical process, the ion is slowly "grown" into the solvent. At the initial stage the ion is present only as a ghost particle and does not interact with the solvent. Afterward, the van der Waals interactions between the ion and the system are reversibly switched on. At the final stage the ion is reversibly charged.

Two processes share essentially identical initial states (ion which does not interact with the solution is equivalent to ion in vacuum) and final states and thus should correspond to

Figure 1. Two hypothetical processes describing solvation free energy of ion. The physical process (shown on top) has (1) ion in vacuum, (2) ion crossing liquid interface, and (3) ion in bulk solvent. The unphysical process (shown on bottom) has (1) ion completely noninteracting with liquid, (2) ion interacting with liquid via van der Waals forces, and (3) ion in bulk solvent. The figure is based on Figure 2.2 from ref 10

identical Gibbs free energy change, which we will refer to as the real solvation free energy ΔG_{real} . This free energy can be formally decomposed into the bulk and surface contributions^{10,20,21,45–47}

$$\Delta G_{\text{real}} = \Delta G_{\text{intr}} + \Delta G_{\text{surf}} \quad (13)$$

The bulk contribution ΔG_{intr} is called the intrinsic solvation free energy and arises from the interaction between the ion and the local solution environment. The surface term ΔG_{surf} arises from the surface polarization, which in turns leads to an electrostatic potential jump of magnitude χ in air to liquid direction. The contribution of the surface term is purely electrostatic and given by the product of the total charge of the molecule Q and the electrostatic potential difference between the initial and the final positions of the molecule.¹⁰ When the outside potential (Volta potential) is 0¹⁹

$$\Delta G_{\text{real}} = \Delta G_{\text{intr}} + \chi Q = \Delta G_{\text{intr}} + \phi_G Q \quad (14)$$

where Q is the total charge of the ion and ϕ_G is the solvent Galvani potential.

Note that physical and unphysical processes result in identical solvation free energies only if the solvent has an explicit surface. If the unphysical process is performed in a system where the whole space is occupied by the solvent, without any boundary between air and liquid, the resulting free energies are intrinsic. Thus, solvation free energies estimated using molecular dynamics with periodic boundary condition and Ewald summation as well as 3D-RISM are, in fact, intrinsic.^{10,19,48}

While solvation free energies obtained from simulation are intrinsic, experimental solvation free energies are usually real.¹⁰ In this article we are using experimental ionic free energies from a Minnesota solvation database.^{49,50} These values were obtained by determining solvation free energies of neutral pairs of ions, ΔG_{pair} , from a thermodynamic cycle. The individual hydration free energies were subsequently obtained by combining the single hydration free energy of proton, measured by Tissandier et al. (265.9 kcal/mol),⁵¹ with ΔG_{pair} . As follows from eq 14, ΔG_{pair} can be decomposed into either intrinsic or real solvation free energies

$$\Delta G_{\text{pair}} = \Delta G_{\text{real,C}} + \Delta G_{\text{real,A}} \\ = \Delta G_{\text{intr,C}} + \Delta G_{\text{intr,A}} + 0 \times \phi_{\text{G}} \quad (15)$$

where subscripts C and A stand for anion and cation. Ultimately, the question of whether the experimental hydration free energies of ions used in this study are real or intrinsic is related to the question of whether the free energy of hydration of a proton is real or intrinsic. A number of articles suggest that the value by Tissandier et al. is real and does contain a contribution from the surface potential.^{50,52,53}

Clearly, if we want to compare results obtained from simulations to experimentally measured solvation free energies, we need to make sure that both sets of energies are either real or intrinsic. Due to difficulties associated with measurement of the experimental Galvani potential,^{10,19} the only way we can make such comparison is by evaluating the Galvani potential from simulations and subsequently converting simulation intrinsic free energies to real ones.

Other authors have named additional arguments supporting the use of ΔG_{real} when discussing simulated results. First, intrinsic solvation free energies depend on the conventional quadrupole moment of the solvent molecule, which is problematic. Lin et al. point out that by embedding an isotropic quadrupole inside the oxygen core one can engineer two water models that will produce identical liquid structure and dynamics but yield arbitrary large differences in ΔG_{intr} (they would also have different ϕ_{G}).¹⁹ The difference will disappear if one considers ΔG_{real} instead.^{10,21,47,48,52,54} In addition, the use of real solvation free energies removes a hotly debated^{13,55–58} difference in the results obtained with P and M summation schemes.¹⁰ We note that these cancellations only occur if both intrinsic solvation free energies and Galvani potential were evaluated using the same theoretical model.

Calculations of Galvani Potential. In this section we discuss ways of evaluating the Galvani potential in both MD and 3D-RISM.

In molecular dynamics ϕ_{G} can be obtained by simulating a liquid droplet in an empty box and integrating the Poisson equation

$$\phi_{\text{G}} = \phi(z_{\text{w}}) - \phi(z_{\text{v}}) = \int_{z_{\text{v}}}^{z_{\text{w}}} dz' z' \langle \rho(z') \rangle \quad (16)$$

where ϕ is the potential relative to infinity, z_{w} and z_{v} are positions deep into liquid and vacuum, respectively, and $\langle \rho(z') \rangle$ is an average charge density at position z . For SPC/E water it has been calculated to be -14.9 kcal/mol/e (-650 mV).⁵²

As simulating the explicit air–water boundary in a standard formulation of 3D-RISM is not possible, a different approach has to be adopted. For an orientationally disordered liquid, the Galvani potential is proportional to the trace of (conventional) quadrupole moment of the solvent molecule (here we are referring to the so-called internal potential).^{10,19,54} For a single-site solvent, the references cited above provide an analytical formula, but for the solvent with multiple sites, the Galvani potential has to be evaluated numerically by calculating the average electrostatic potential in the center of a small cavity (hard sphere).^{10,19} A small, hard cavity ensures that there is no significant perturbation of liquid near the surface of the cavity and that the only contribution to the potential inside the sphere is due to the quadrupole moment (extensive discussion regarding this can be found in section 4.3.8 of ref 10).

It was shown that this approximation is relatively correct for water at room temperature.¹³ In 3D-RISM the electrostatic potential at a given point can be calculated using⁵⁹

$$\phi(\mathbf{r}_0) = \frac{1}{4\pi\epsilon_0} \sum_{\alpha=1}^{n_s} \int_V \frac{g_{\alpha}(\mathbf{r}) \rho_{\alpha} q_{\alpha}}{r} d\mathbf{r} \quad (17)$$

where r is the distance from $\mathbf{r}_0$ to $\mathbf{r}$, ϵ_0 is the permittivity of vacuum, $g_{\alpha}(r) = h_{\alpha}(r) + 1$, ρ_{α} is the number density of the site α , and q_{α} is the partial charge of the site α . The Galvani potential of the solvent was estimated by calculating $\phi(\mathbf{r}_0)$ in the center of the cavity. Using the radius of the cavity equal to 0.5 Å (same as grid size), we estimated ϕ_{G} to be -13.43 kcal/mol/e for cSPC/e water and -12.55 kcal/mol/e for cTIP3P water.

Finite-Size Corrections. 3D-RISM is implemented on a nonperiodic grid and, therefore, corresponds to an infinitely diluted solute.⁶⁰ However, in PBC/Ewald MD simulations a solvated ion interacts with its periodic images; this introduces a number of periodicity related artifacts (finite-size effects).^{12,13,61–63} For single atomic ions there are analytical formulas which let one correct free energies resulting from MD simulation to reflect solvation in a nonperiodic system.^{10,13} For polyatomic ions there are no analytical formulas and one has to run two Poisson–Boltzmann simulations for periodic and nonperiodic systems to quantify the energetic effect of periodicity.^{63,64}

Fortunately, the magnitude of most of these errors scales as the ratio of the molecule size to the box length and becomes unimportant in the large box limit. A way to correct the finite-size errors without resorting to periodic Poisson–Boltzmann calculations has been suggested in the paper by Rocklin et al.⁶³

$$\Delta\Delta G_{\text{ANA}} = \Delta\Delta G_{\text{NET}} + \Delta\Delta G_{\text{USV}} + \Delta\Delta G_{\text{RIP}} + \Delta\Delta G_{\text{EMP}} \quad (18)$$

where $\Delta\Delta G_{\text{ANA}}$ stands for analytical corrections, $\Delta\Delta G_{\text{NET}}$ accounts for periodicity-induced net charge interaction, $\Delta\Delta G_{\text{USV}}$ is for periodicity-induced undersolvation, and $\Delta\Delta G_{\text{RIP}}$ is for residual integrated potential effects. $\Delta\Delta G_{\text{EMP}}$ is an empirical term. Out of all these corrections only two scale as an inverse length of the box L : $\Delta\Delta G_{\text{NET}}$ and $\Delta\Delta G_{\text{USV}}$. All other correction terms either decrease rapidly with increasing box size or become significant only for situations involving binding of charged species. Note that there is no need for us to correct the error associated with P summation since we are combining intrinsic free energies with ϕ_{G} , which leads to cancellation of this error.¹⁰

As we used a large box, only $\Delta\Delta G_{\text{NET}}$ and $\Delta\Delta G_{\text{USV}}$ were taken into account. All ionic hydration free energies obtained from molecular dynamics simulations were corrected as⁶³

$$\Delta G_{\text{MD,cor}} = \Delta G_{\text{MD}} + \Delta\Delta G_{\text{USV}} + \Delta\Delta G_{\text{NET}} \\ = \Delta G_{\text{MD}} - \frac{\xi}{8\pi\epsilon_0\epsilon_{\text{w}}} \frac{Q^2}{L} \quad (19)$$

where ξ is the Wigner integration constant for cubic boxes (≈ -2.837297),⁶⁵ ϵ_{w} is the permittivity of model water (73.5 for SPC/E), and Q is the total charge of molecule. A similar shortened correction scheme has been used in other recent publications.^{19,66} We note that with the settings which were used in our study (3 nm sized box), the final finite-size correction is quite small, around 0.2 kcal/mol, and much

smaller than the contribution due to water–vacuum potential jump.

METHODOLOGY

Experimental hydration free energies of ionic compounds and their geometries were taken from the 2012 version of the Minnesota solvation database.^{49,50} These values are based on the hydration free energy of a proton = 265.9 kcal/mol.⁵¹ When selecting compounds from the database we avoided water clusters as well as ions that were structurally similar to other chosen molecules. We ended up selecting 70 compounds in total: 36 anions and 34 cations.

For the ionic data set, we assigned GAFF force field parameters and AM1-BCC charges using various programs from the AmberTools 14 package.⁶⁷ We also tested the performance of OPLS-2005⁶⁸ Lennard–Jones parameters combined with Charge Model 5 partial charges (CM5).⁶⁹ Assignment of OPLS-2005 parameters was performed automatically using Maestro.⁷⁰ For all calculations we used Lorentz–Berthelot mixing rules.⁷¹ Evaluation of CM5 charges required additional quantum mechanical calculations, which were performed with Gaussian 09, Revision D.01,⁷² using the M06-2X functional⁷³ and MG3S basis set.⁷⁴ Solvent was represented using the SMD model.⁷ Charges were extracted from output files using CMSPAC program.⁷⁵

Molecular dynamics simulations with ionic compounds were performed using Gromacs 5.04.⁷⁶ We used a cubic box with periodic boundary conditions. The water was represented using a rigid SPC/E model.⁷⁷ In all simulations the system consisted of a single ion and 1024 water molecules; no counterions were used. All bonds with hydrogens were kept rigid using the LINCS algorithm of 12th order. Dynamics was simulated using the Langevin integrator, with a reference temperature of 298.15 K and a friction constant of 1.0 ps^{−1}.

For short-range interactions a pair list was generated using a Verlet cutoff scheme. Lennard–Jones interactions were smoothly switched off between 9 and 12 Å. The cutoff artifacts were accounted for using long-range pressure and dispersion corrections as implemented in Gromacs. Electrostatics interactions were treated using the particle-mesh Ewald (PME) method⁷⁹ with a 12 Å real space cutoff, 1.2 Å Fourier spacing, 6th order spline interpolation, and tolerance set to 10^{−6}.

To compute the hydration free energy using MD, we performed 20 separate calculations at each λ , decoupling first electrostatics and then Lennard–Jones interactions between solute and solvent. Intramolecular interactions within solute were kept the same at all lambda values. Calculations with modified electrostatics interactions were performed at $\lambda = 0$, 0.25, 0.5, 0.75, and 1. Decoupling of the Lennard–Jones interactions was done using calculations at $\lambda = 0$, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.65, 0.7, 0.75, 0.8, 0.85, 0.9, 0.95, and 1.0.

Prior to running MD simulation at each λ , we performed 5000 steps of steepest descent optimization. After that we performed a 200 ps equilibration and 1300 ps production run. The time step was set to 1 fs. In both equilibration and production runs, pressure was kept constant at 1 bar using a Berendsen barosta,⁸⁰ with time constant set to 1 ps and compressibility to 4.5 × 10^{−5} bar^{−1}.

After completing the simulations, the intrinsic hydration free energy was evaluated using the Multistate Bennett Acceptance Ratio (MBAR).²⁹ The actual calculation was performed using a python script `alchemical-analysis.py`.³¹

RISM calculations were performed with SPC/E and TIP3P water models that have Lennard–Jones parameters on hydrogen to improve convergence (cSPC/E and cTIP3P).⁸¹ Water susceptibility functions were generated using dielectrically consistent 1D-RISM (DRISM)⁸² implemented in the AmberTools 14 package. Water density was set to 997 kg/m³ and dielectric constant to 78.4 (experimental values at 298 K). The DRISM equations were solved with tolerance set to 1 × 10^{−12} and grid spacing to 0.025 Å.

3D-RISM calculations were performed using the `rism3d.snglpnt` program from the AmberTools 14 package.^{22,81,83} The grid spacing was set to 0.5 Å, buffer to 25 Å, and tolerance to 1 × 10^{−5}. While these parameters provide slightly less accurate results compared to the ones used in our previous work,¹⁸ the resulting errors in obtained hydration free energies are only around 0.1 kcal/mol. On the other hand, they led to a decrease in calculation time from minutes to seconds, which in our opinion is a favorable trade-off. Both 1D-RISM and 3D-RISM calculations were performed using the PSE-3 closure. Similarly to our previous work, calculation setup was automated using a Python script available at https://github.com/MTS-Strathclyde/PC_plus.

RESULTS AND DISCUSSION

PC+ Model Verification. Figure 2 compares insertion, charging, and hydration free energies from 3D-RISM/PSE-3/

Figure 2. Comparison of predicted insertion free energies (top), charging free energies (middle), and hydration free energies (bottom) of ionic compounds from MD and PSE-3/PC+. In both models, solutes were described using GAFF parameters and AM1-BCC charges. Anions are shown as red circles and cations as blue triangles. All energies are in kcal/mol. The box in the top left corner of each figure shows root-mean-square error (RMSE), standard deviation (SD), and bias of PSE-3/PC+ results compared to MD.

PC+ (from here on simply PC+) and MD/MBAR (or simply MD), both obtained using GAFF parameters, AM1-BCC charges, and SPC/E water models (cSPC/E for 3D-RISM). Both charging and hydration energies include the water–vacuum potential as well as finite-size corrections for MD results. The PC+ model underestimates insertion free energies with respect to MD, but the errors are systematic and proportional to the magnitude of the energy, unlike errors from the PSE-3 closure alone that are more or less random and are much larger in magnitude (uncorrected results are included in the Supporting Information). On the other hand, the agreement between charging free energies from both models is good, with errors of about 1.3 kcal/mol. Since the charging free energies are much larger in magnitude than insertion free energies, hydration free energies are in close agreement. Very similar results, but for neutral compounds, have also been obtained by Kleine et al.⁸⁴

Importantly, these results also justify our choice of approximating ϕ_G for 3D-RISM. Uncorrected results, which can be found in the Supporting Information, consistently overestimate the hydration free energy of anions and underestimate energies of cations compared to MD by about 2 kcal/mol. Corrected results still contain charge-dependent bias, but it is much smaller: around 0.4 kcal/mol.

Both 3D-RISM and MD free energies have associated uncertainties, but with the parameters we used they are quite small: about 0.08 kcal/mol on average for MD and less than 0.01 kcal/mol for 3D-RISM. These uncertainties are much smaller than errors associated with models and can be safely ignored for the purposes of this study.

The extent of agreement of PC+ results with MD is quite remarkable, considering that for ionic compounds energies are much larger in magnitude compared to neutral compounds. The observed differences can be attributed to the fact that 3D-RISM uses approximate closure, assumes additivity of direct correlation functions, omits third and higher order correlation functions, and does not sample solute conformations (this problem, however, can be solved by MD/3D-RISM⁸⁵). Overall, these results show that PSE-3/PC+ can serve as a good approximation to the much more expensive MD method: hydration free energies with 3D-RISM using parameters used in this study are evaluated in seconds on a single CPU, compared to approximately 6 h on 12 CPUs needed to obtain a single free energy from MD. This equates to about 4 orders of magnitude difference in computational power in favor of RISM.

Comparison with Experiment. Figure 3 shows a comparison between predicted and experimental solvation free energies. The two top graphs compare results from MD and PSE-3/PC+ obtained with GAFF/AM1-BCC parameters to experiment. The difference of errors from PSE-3/PC+ and MD is also much smaller than the difference between the two models themselves. Thus, for a number of molecules PSE-3/PC+ predicts hydration free energies more accurately than molecular dynamics. This might seem surprising at first, considering that 3D-RISM contains additional sources of errors due to a number of approximations. However, it has been shown that extra Lennard–Jones parameters on hydrogen in the cSPC/E model partially take into account polarization,⁸¹ which might compensate for additional errors due to the model.

The accuracy of the results above is surprising and indicates that hydration free energies obtained with classical point charge models can be relatively reliable even without taking into account polarization, charge transfer, and an accurate

Figure 3. Comparison of hydration free energies of ionic compounds against experiment. (Top and middle) Results by MD and PSE-3/PC+, obtained using GAFF/AM1-BCC parameters. (Bottom) Results from PSE-3/PC+, obtained with OPLS/CM5 parameters.

representation of dispersion interactions. Moreover, they further support the use of “real” hydration free energy as opposed to intrinsic (uncorrected results are provided in the Supporting Information and show clear biases for anions and cations).

To test whether we can improve our estimates using different Lennard–Jones parameters and partial charges, we repeated the 3D-RISM calculations using combinations of the OPLS-2005 force field Lennard–Jones parameters and CM5 charges. We also reran all 3D-RISM calculations with cTIP3P water model, which was intended as a test for both PC+ and Galvani corrections. These results are shown in Table 1, where we additionally presented errors for cations and anions separately.

On the basis of the results in Table 1, we see that OPLS/CM5 parameters outperform GAFF/AM1-BCC for both cSPC/E and cTIP3P water; individual data points obtained with these parameters and cSPC/E water are shown on the bottom graph of Figure 3. For both sets of nonbonded parameters cTIP3P results are slightly worse than cSPC/E. It is interesting that all models overestimate hydration free energy compared to experiment, similarly to the results obtained with the SMD model.⁷

Compared to GAFF/AM1-BCC, OPLS/CM5 lowers both random error and bias, which is expected considering that this model was parametrized in order to accurately reproduce the electric field of a molecule and uses a more sophisticated electronic structure method to do it. This suggests that the use of QM/3D-RISM that has been proposed and implemented by a couple of other groups might lead to even better results.^{86,87}

To our knowledge the approach presented here is one of the most accurate ways of predicting ionic hydration free energies through computational models. The RMSE of about 3 kcal/mol

Table 1. Comparison of Predicted Hydration Free Energies with Experimental Data (kcal/mol)

method	force field	water model	combined			cations			anions		
			RMSE	SD	bias	RMSE	SD	bias	RMSE	SD	bias
MD	GAFF/AM1-BCC	SPC/E	4.76	3.61	3.13	4.43	2.28	3.82	5.05	4.46	2.47
PC+	GAFF/AM1-BCC	cSPC/E	4.84	3.79	3.04	3.93	2.24	3.25	5.56	4.84	2.85
PC+	OPLS/CM5	cSPC/E	2.94	2.87	0.73	2.41	2.07	1.27	3.37	3.41	0.22
PC+	GAFF/AM1-BCC	cTIP3P	5.40	3.85	3.82	3.50	2.19	2.76	6.72	4.75	4.82
PC+	OPLS/CM5	cTIP3P	3.20	2.87	1.45	2.28	2.07	1.02	3.87	3.44	1.86

obtained with OPLS/CM5 parameters and the cSPC/E water model is comparable to the 3.25 kcal/mol mean unsigned error reported for the SMVLE model, albeit on a larger data set.⁸ The approach also outperforms other popular models such as SMD⁷ and SM8.⁸⁸ Importantly, the results presented here are obtained with force fields, which have not been parametrized for ionic solvation free energies. Therefore, they can be further improved by optimizing the force field parameters that is the subject of our ongoing research.

CONCLUSION

We proposed a new method for estimating the Galvani potential using 3D-RISM. The obtained estimate is then used to compute real hydration free energies of molecular ions with 3D-RISM/PSE-3/PC+ models. Our values are in close agreement with both results of direct simulation by force field-based MD and with real experimental free energies. We found that the major source of errors in our calculations was related to the force field parameters and atomic partial charges and not to the approximations used in the 3D-RISM model. The use of OPLS-2005 Lennard–Jones parameters and CM5 partial charges substantially decreased disagreement between the 3D-RISM hydration free energies and experiment, bringing the root-mean-square error on a set of 36 anions and 34 cations to about 3 kcal/mol. This level of accuracy makes the method proposed here competitive with the state of the art MD and continuum solvation approaches.^{8,88}

This study, together with our previous results for neutral compounds,¹⁸ shows that 3D-RISM, combined with PSE-3 closure and PC+ correction, is a powerful method for predicting thermodynamic parameters of molecular solvation. The results suggest that at least for ionic compounds the accuracy of the 3D-RISM/PSE-3/PC+ model is more limited by the accuracy of the force fields than by the model approximations. A better parametrization of the force fields (potentially using fast 3D-RISM calculations for high-throughput optimization of parameters) should further reduce the observed errors. The study also revealed a problem related to the PC+ correction—systematic underestimation of the vdW component of the hydration free energy; we plan to address this problem in future articles.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpcb.5b10809.

Tables with experimental and computed hydration free energies for both data sets (csv); pdb structures of all molecules used in the calculations (zip); results obtained without taking into account Galvani potential or PC+ correction are also presented (pdf).

AUTHOR INFORMATION

Corresponding Authors

*E-mail: maxim.fedorov@strath.ac.uk.

*E-mail: david.palmer@strath.ac.uk.

Notes

The authors declare no competing financial interest.

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